UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,295	09/11/2003	Wolf-Ruediger Schaebitz	242650US0CONT	6092

22850 7590 01/29/2007

OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,295	SCHAEBITZ ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-105* is/are pending in the application.

4a) Of the above claim(s) *20-100,103 and 104* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,101,102 and 105* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/04; 2/05; 6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, (claims 1-19, 101-102 and 105) in the reply filed on 23 October 2006 is acknowledged. The traversal is on the ground(s) that adequate reasons and/or examples have not been provided to support a conclusion of patentable distinctness between the identified groups and further, on the grounds that the Office has not shown that a burden exist in searching all of the claims. This is not found persuasive because the Examiner provided a detailed explanation of why the inventions were distinct, namely that methods of treatment, such as administering polypeptides, polynucleotides and neural stem cells are not obvious variants, i.e., prior art anticipating one type of treatment would not render obvious another type of treatment. The same reasoning is true for the screening methods. Because of this, there is an extension of search necessary for each additional invention (of which there are 12) and that would present a serious burden. Furthermore, the issues regarding enablement are very different for the different methods, thus, not only is there a search burden in the literature, but there is an examination burden with respect to issues under 35 U.S.C. 112, first paragraph. See the restriction requirement mailed 23 May 2006 for further details.

The requirement is still deemed proper and is therefore made FINAL.

Claims 20-100 and 103-104 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 23 October 2006:

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 101-102 and 105 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of GMCSF or GCSF, erythropoietin (EPO) for the treatment of stroke or cerebral ischemia and diseases enabled by the prior art, does not reasonably provide enablement for the methods as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the

existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claims are extremely broad. With respect to the recitation of GMCSF, GCSF or derivatives thereof (all claims), while it is recognized that derivatives of these hematopoietic factors are known in the art, and Applicants do provide a listing of possible muteins (for example, for GSCF, see p. 21-24; for GMCSF, see 26-27), Applicants' own definition of derivatives encompass low molecular weight compounds (p. 22) and muteins having only 20-95% homology with the native proteins. In this case, the definition of derivatives provided by Applicants in the specification encompass almost any agent, including those yet to be discovered. The claims reciting GCSF, GMCSF or derivatives thereof amount to single means claims. Single means claims are those that cover every conceivable means for achieving the stated purpose. Single means claims are nonenabling for the scope of the claim because the specification discloses at most only those means known to the inventor, in this case, GCSF or GMCSF. When claims depend on a recited property, i.e, the ability to treat a neurological condition in this case, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See MPEP 2164.08(a).

In general, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are

generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions, i.e., how could a CSF having only 20% homology be functionally capable of carrying out the method steps.

Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is

dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

In addition, claim 11 recites administration with a "hemodynamically active compound." Hemodynamics is the study of properties and flow of blood. This claim encompasses almost any agent prescribed for vascular disease, thus the scope of the claim is not commensurate with what is disclosed in the specification, namely the administration of tPA in the treatment of stroke. Similarly, with regard to claims 13 and 14, Applicants recite agents that facilitate passage over the blood brain barrier and anti-apoptotic agents, respectively. Applicants suggest protein transduction domains or TAT sequences as possible carriers and bradykinin administration to aid delivery of therapeutics into the brain (see p. 27, last paragraph to p. 28, 1st paragraph), however, the claim is not commensurate in scope with Applicants' disclosure, as it encompasses agents yet to be discovered. Likewise claim 14 encompasses any possible anti-apoptotic agent, whereas Applicants disclose caspase inhibitors.

The state of the art is complex. For instance, Bath et al. (Cochrane Database Syst Rev. 2006; 3: CD0005207: 1-13) teach that as of 2006 no large trials of EPO, GCSF or other CSFs have been performed and it is too early to know whether CSFs

improve functional outcome in stroke (see abstract), thus underscoring the inherent complexity and unpredictability within the art. Moreover, the prior art is silent with respect to the treatment of Parkinson's disease, amyotrophic lateral sclerosis or neurotrauma with the claimed methods (claim 8). In addition, the specification contemplates treatment of schizophrenia, but a search of schizophrenia and colony stimulating factors reveals that CSFs are only used in the treatment clozapine-induced agranulocytosis (see, for instance, Hagg et al. Int Clin Psychopharmacol. 2003; 18: 173-174). In addition, with regard to the administration of tPA, while it is well known in the art that tPA administered within 3 hours following stroke symptoms onset can be beneficial in some stroke patients, claims 11-12 encompass administration of tPA for any neurological condition, and tPA is not indicated for any neurological condition. Furthermore, the specification discloses reasoning that supports not to giving a hemodynamically active compound to treat any neurological disease or stroke at paragraph [0084]:

> An objective, retrospective review of 358 carotid endarterectomies performed in the neurosurgical teaching units of the University of Toronto in the year 1982 demonstrated a perioperative stroke rate of 3.9% and a death rate of 1.5%. Most (82%) surgical neurological complications occurred after the immediate post-operative period (24 hours). This high incidence of delayed stroke suggests that most perioperative strokes <u>are embolic rather than hemodynamic.</u> (Emphasis added).

However, claim 11 encompasses administration of a hemodynamically active compound for the treatment of any neurological disorder.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity in

treating the neurological condition, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and which neurological conditions can be treated, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 3, 5, 6, 7, 9, 10, 17, 18, 101 and 105 are rejected under 35 U.S.C. 102(b) as being anticipated by Takeshi et al. (JP5246885A2, published 26 December 1991—provided on Applicants' 1449 form. Translation also provided by Applicants).

The claims are drawn to a method of treating a neurological condition in a mammal, comprising administering to the mammal a hematopoietic factor selected from the group consisting of GMCSF, a GMCSF derivative, GCSF, a GCSF derivative, and combinations thereof in an amount sufficient to treat the neurological condition (1), wherein said neurological condition is selected from the group consisting of neurological disease with pathophysiological mechanisms involving ischemia, a neurological disease with pathophysiological mechanisms involving hypoxia, a neurodegenerative disease, and a disease of the nervous system accompanied by neural cell death (2), wherein the neurological condition is neurological disease with pathophysiological mechanisms involving ischemia or hypoxia (3), further comprising administering one or more additional hematopoietic factors (5), wherein the additional hematopoietic factors are selected from the group consisting of a macrophage stimulating factor, an interleukin, and erythropoietin (6), wherein GCSF and erythropoietin are administered to the mammal (7), wherein the hematopoietic factor is GCSF or a GCSF derivative (9), wherein the hematopoietic factor is GMCSF or a GMCSF derivative (10), wherein the hematopoietic factor is a human factor or derived from a human factor (17), wherein the mammal is human (18) wherein the hematopoietic factor is administered by one or more modes of administration selected from the group consisting of direct intracerebral injection, intravenously, intraarterially, orally, and subcutaneously (19); a method of enhancing the viability of a neural cell culture comprising contacting the neural cell culture with a hematopoietic factor selected from the group consisting of GMCSF, a GMCSF derivative, GCSF, a GCSF derivative, and combinations thereof in an amount

sufficient to enhance the viability of the neural cell culture relative to the culture prior to contacting with the hematopoietic factor (101); a method of treating a neurological condition in a mammal, comprising administering to the mammal a hematopoietic factor selected from the group consisting of GMCSF, a GMCSF derivative, GCSF, a GCSF derivative, and combinations thereof in an amount sufficient to treat the neurological condition via stimulation of adult neuronal stem cells (105).

Takeshi teach the administration of GCSF, GMCSF, and/or EPO for the treatment of cerebral vascular dementia or Alzheimers' Disease or AD (see claims 1-3; paragraphs [0002], [0005], [0006]), which are both neurological disorders. Vascular dementia is associated with cerebral ischemia (see paragraph [0002]). Takeshi also teach that the GCSF, GMCSF and/or EPO are human in origin, and since the treatment of dementia and AD are contemplated, the treatment of humans is also contemplated (see paragraphs [0009], [0010], [0015]). Takeshi teach administration via intracerebral or intravenous injection (see paragraphs [0012], [0013]). Takeshi also contemplate the administration of GCSF to primary cell neural cultures (see paragraphs [0015]). Because Takeshi teach the administration of the same compounds to the same patient populations, namely humans and neural cell cultures, the effects of treating neurological conditions via stimulation of adult neuronal stem cells (claim 105) and to enhance the viability of the neural cell culture relative to the culture prior to contacting with the hematopoietic factor (claim 101) the methods of Takeshi would inherently have the same effects, thus the claims do not contribute anything over the prior art

Claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 18, 19 and 105 are rejected under 35 U.S.C. 102(b) as being anticipated by Buschmann et al. (WO 99/17798—provided by Applicants' on 1449 form).

In addition to what is discussed above in the rejection over Takeshi, the claims are further drawn to the method of claim 3, wherein the neurological disease is stroke (4, 8), Parkinson's disease, amyotrophic lateral sclerosis, neurotrauma, cerebral ischemia due to cardiac arrest or cerebral ischemia during an operative procedure (8).

Buschmann et al. teach the administration of GMCSF and/or GCSF (either alone or in combination) via intravenous or peritoneal injection for the treatment of vascular disease or cardiac infarct or stroke (see p. 8, lines whole page; p. 10, 1st paragraph). Buschmann et al. contemplate the treatment of humans (see p. 18, 2nd paragraph). Because Buschmann et al. teach the administration of the same compounds to the same patient population, namely humans suffering from cerebral ischemia, stroke, cardiac infarct, etc., the effects of treating neurological conditions via stimulation of adult neuronal stem cells (claim 105) inherent to the their methods, thus the claims do not contribute anything over the prior art.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 3, 4, 8, 9, 10, 17, 18, 19, 101 and 105 are rejected under 35 U.S.C. 102(e) as being anticipated by Chajut (US 2002-0198150 A1—listed on Applicants' 1449 form—filed 7 June 2002, and also claiming priority to provisional application 60/296,585, filed 7 June 2001).

In addition to what is discussed above in the rejection over Takeshi, the claims are further drawn to the method of claim 3, wherein the neurological disease is stroke (4, 8), Parkinson's disease, amyotrophic lateral sclerosis, neurotrauma, cerebral ischemia due to cardiac arrest or cerebral ischemia during an operative procedure (8).

Chajut teaches a method of administering GCSF, GMCSF, IL-3 or IL-6 (see paragraph [0028]) for the purpose of treating ischemia, stroke or myocardial infarct, to name a few (see, for example, claims 1-17, paragraphs: [0025]; [0033]). Chajut also teaches injection via subcutaneous, transdermal, intravenous, intramuscular, intrathecal, and other parenteral routes of administration (see paragraph [0058]). Chajut teaches administration to humans and contemplates many types of CSFs, including those of human origin (see, for example [0042], [0059]). Chajut also contemplates the utility of claimed methods (administration of CSFs) as resulting in the mobilization of stem cells, for improving clinical and functional outcome after tissue trauma and for inducing organ regeneration in animals, including humans (see paragraph [0052]). Finally, Chajut discloses that the administration of CSFs to stem cells in culture increases their viability (see paragraph [0077]). Support for all of these

elements can also be found in the provisional application, 60/296,585, filed 7 June 2001.

Claims 1, 2, 3, 4, 8, 9, 11, 12, 15, 16, 17, 18 and 105 rejected under 35 U.S.C. 102(a) as being anticipated by DE 100 33 219 A1 (published 24, January 2002, 7 days before the effective filing date of the instant application—listed on Applicants' 1449 form, translation of the relevant pages also provided by Applicant). In addition to what is discussed above in the rejection over Takeshi, the claims are further drawn to the method of claim 3, wherein the neurological disease is stroke (4, 8, 15), Parkinson's disease, amyotrophic lateral sclerosis, neurotrauma, cerebral ischemia due to cardiac arrest or cerebral ischemia during an operative procedure (8), which further comprises administration of a hemodynamically active compound (11) or tissue plasminogen activator or tPA (12).

The DE 100 33 219 document teaches the administration of human-derived GCSF to patients having suffered a stroke (claims 1-7 and paragraphs [0002], [0004], [0005]). The '219 document also teaches that tPA can be administered in the therapeutic window of 3-6 hours following stroke (paragraph [0002]). Because the '219 document teaches the administration of the same compounds to the same patient population, namely humans suffering from cerebral ischemia, neurological disease or stroke, etc., the effects of treating neurological conditions via stimulation of adult neuronal stem cells (claim 105) inherent to the their methods, thus the claims do not contribute anything over the prior art.

Claim 101 is rejected under 35 U.S.C. 102(b) as being anticipated by Konishi et al. (Brain Res. 1993; 609: 29-35—provided by Applicant on 1449 form). The claims is drawn to a method of enhancing viability of a neural cell culture comprising contacting the neural cell culture with a hematopoietic factor selected from the group consisting of GMCSF, a GMCSF derivative, GCSF, a GCSF derivative and combinations thereof in an amount sufficient to enhance viability of the neural cell culture relative to the culture prior to contacting with the hematopoetic factor.

Konishi et al. teach that GCSF and GMCSF increased choline acetyltrasferaste activity in primary cultured mouse septal neurons (see p. 29, right column, 1st paragraph; p. 30, Table I), which encompasses enhancing viability of claim 101.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 18, 19 and 105 in the rejection under 35 U.S.C. 102(b) discussed above, and further in view of Siren et al. (Eur Arch Psychiatry Clin Neurosci. 2001; 251: 179-184).

In addition to what is discussed above the claims are further drawn to administering an additional hematopoietic factor that is EPO (claim 6) and that the hematopoietic factor is derived from a human factor (17).

The teachings of Buschmann et al. are outlined above and are applicable here. Buschmann et al. do not specifically state that they used a human derived hematopoietic factor. However, Buschmann et al. do contemplate the treatment of humans (as discussed above) and it would be obvious to use human-derived factors in the treatment of humans. In addition, with regard to claim 19, although Buschmann et al. do not specifically teach intracerebral administration of the hematopoetic factor(s), it would be obvious to do this since they contemplate treatment of stroke (i.e. brain injury) and intracerebral administraton would bypass the blood brain barrier. Furthermore, Buschmann et al. do not teach the administration of an additional hematopoietic factor

which is EPO. Siren et al. teach at p. 182, right column, last paragraph to p. 183, left column, 1st paragraph that:

> The experimental data reviewed above demonstrate multiple neuroprotective mechanisms of action of EPO. These findings together with the fact that EPO and EPOR are expressed in the human central nervous system,...and that EPO is an extremely well-tolerated compound, used in millions of patients...,strongly support evaluation of EPO for neuroprotective therapy in a clinical setting. The therapeutic potential of this agent ranges from stroke and neurodegenerative diseases (Parkinson syndrome, Alzheimer's diseases, amyotrophic lateral sclerosis) to psychiatric applications such as schizophrenia; where neurodegenerative processes are likely to contribute to the pathophysiology of the disease...The initial safety study has been complete with promising results demonstrating that intravenously administered EPO is able to enter the brain in acute human stroke victims and that the EPO treatment is extremely safe in stroke patients.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. by administering EPO for the treatment of stroke, as taught in Siren et al. because Siren et al. report success in their clinical trial in the treatment of stroke with EPO. The person of ordinary skill in the art would have been motivated to make the substitution because according to Siren et al. neuroprotection as a means to oppose pathological neuronal loss in diseases such as stroke is an approach that is well supported by data in the neuroscience field and administration of multiple factors that oppose neuronal loss would be beneficial. In addition, Buschmann et al. teach that the administration of CSFs leads to an increase in collateral vessels, which would improve outcome of diseases characterized by ischemia, such as stroke. Finally, Buschmann also teach that there is a need in the art for approaches to treating stroke or ischemic disease (p. 3, 2nd paragraph). Furthermore, the person of ordinary skill in the art could have reasonably expected

success because both Buschmann et al. and Siren et al. report success in their methods. The combined teachings of Buschmann et al. and Siren et al. teach the administration of the same compounds to the same patient population, thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 16, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited above) and Siren et al. (cited above) as applied to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 18, 19 and 105, above, and further in view of del Zoppo GJ, Curr Opin Hematol. 2000; 7:309-15).

In addition to what is discussed above the claims are further drawn to administering a hemodynamically active compound (11), tPA (12, 16), wherein the condition is stroke (15).

The combined teachings of Buschmann et al. and Siren et al. are discussed above and are applicable here. The combined teachings of Buschmann et al. and Siren et al. do not teach the administration of tPA. del Zoppo teaches that as of the the time of the invention (late 2000), tPA is the only agent licensed for clinical use in cases of acute ischemic stroke, (p. 311, left column, 2nd full paragraph). Because tPA breaks up clots, this relates to hemodynamics, or blood flow, thus the limitations of claim 11 are met. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. and Siren et al. by administering tPA to stroke victims, as taught in del Zoppo because according to del

Zoppo, despite the clinical indications and patient limitations in the administration of tPA, tPA administration within 3 hours of stroke symptom onset increases the likelihood of no or minimal residual neurological outcome (see p. 313, right column, last paragraph), i.e., there are risks but the benefits to certain patients (minimal or no negative neurological outcome) recommend tPA for use in certain clinical cases of stroke. The person of ordinary skill in the art would have been motivated to combine the teachings because as outlined above, there are only a limited number of available options for the clinician in the treatment of stroke. Secondly, as outlined in del Zoppo, tPA administration is the only licensed therapy for ischemic stroke, but, there are risks involved in tPA treatment, thus providing a strong motivation in the art to combine treatment with other, possibly more benign treatments, as outlined in the teachings of Buschmann et al. and Siren et al. Furthermore, the person of ordinary skill in the art could have reasonably expected success because both Buschmann et al. and Siren et al. report success in their methods, and tPA was already used in the art in certain circumstances for the treatment of stroke. The combined teachings of Buschmann et al., Siren et al. and del Zoppo teach the administration of the same compounds to the same patient population, thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 13, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—cited

above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 17, 18, 19 and 10 above and further in view of Emerich et al., Clin Pharmacokinet. 2001; 40: 105-23.

In addition to what is discussed above the claims are further drawn to administering a compound that facilitates passage over the blood brain barrier (13).

The teachings of Buschmann et al. are discussed above and are applicable here. Buschmann et al. do not teach administering an agent that facilitates passage over the blood brain barrier (BBB). Emerich et al. teach that the agent Labradimil has been successfully developed to increase the permeability of the BBB (see for example, p. 119, left column, last paragraph, under "Clinical Results")). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. by administering labradimil as taught in Emerich et al. because Buschmann et al. teach administering CSFs via intraperitoneal or intravenous injection and they contemplate the treatment of cerebral ischemia and stroke (discussed above), however, it is well known in the art that the BBB acts as a barrier to drugs getting to the brain (see for instance, Emerich et al., p. 106, right column, last paragraph). Emerich et al. remedies this deficiency and bypasses the need for direct intracerebral injection of CSFs by co-administering labradimil to temporarily increase the permability of the BBB to drugs. The person of ordinary skill in the art would have been motivated to administer labradimil because it is well known that the BBB is a barrier to getting drugs to the brain and direct intracerebral injection is uncomforable. Emerich et al. state at p. 106, right column, last paragraph: "[b]ecause only a fraction of all bioactive drugs possess the attributes required to penetrate the BBB, the treatment of CNS

disease could be improved if a means were available to safely and reversibly modulate the permeability of the BBB to allow greater drug distribution to the CNS." Furthermore, the person of ordinary skill in the art could have reasonably expected success because Emerich et al. teach that labradimil permeabilizes the BBB and could potentially be used to increase delivery of agents without increasing dosage (see abstract; citation above). Thus the claims do not contribute anything non-obvious over the prior art.

Claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 14, 17, 18, 19 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buschmann et al. (WO 99/17798—(cited above) as applied to claims 1, 2, 3, 4, 5, 6, 8, 9, 10, 17, 18, 19 and 105 above and further in view of Tarkowski et al. (Stroke. 1999; 30: 321-327—listed on Applicants' 1449 form) and Lu et al. (Neurobiology of Disease. 2001; 8: 194-206).

In addition to what is discussed above the claims are further drawn to administering an anti-apoptotic compound (14).

The teachings of Buschmann et al. are discussed above and are applicable here. Buschmann et al. do not teach the additional administration of anti-apoptotic factors. Tarkowski et al. teach that there is decrease in expression of anti-apoptotic proteins in the cerebrospinal fluid of stroke victims (see p. 325, right column, last paragraph) and concluded that controlling or down-regulating pro-apoptotic factors might decrease brain damage in stroke victims (p. 326, right column, last paragraph). In addition, Lu et al. teach that caspase inhibition in combination with glutamate receptor antagonists (in order to decrease excitotoxic necrosis) could be used to decrease apoptosis and

necrosis of neurons following stroke (see p. 204, last paragraph). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Buschmann et al. by administering agents that control apoptotic and necrotic cell death, as taught in Tarkowski et al. and Lu et al. because apoptosis of neurons is thought to contribute to neuronal cell death (see Tarkowski, p. 325, right column, last paragraph to p. 326, left column, 1st paragraph). The person of ordinary skill in the art would have been motivated to combine the teachings because as outlined above, there are only a limited number of available options for the clinician in the treatment of stroke. Furthermore, the person of ordinary skill in the art could have reasonably expected success because Lu et al. provide further evidence of how caspase inhibition (and decreasing apoptosis) combined with glutamate receptor antagonism (to prevent necrosis) could lead to less neuronal loss following ischemic injury and neurodegenerative disorders. Thus the claims do not contribute anything non-obvious over the prior art.

Claims 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Konishi et al. (cited above).

In addition to what is discussed above the claims are further drawn to a neural cell culture that is a neural stem cell culture (102).

The teachings of Konishi et al. with regard to their effects on primary cultured mouse septal neurons are discussed above (claim 101). Konishi et al. do not specifically teach using a neural stem cell culture (claim 102). However, they do state

at p. 29, right column, 1st paragraph that "[these] hematopoetic factors regulate the differentiation and proliferation of pluripotent hematopoetic progenitors and stem cells," and they teach the optimal concentrations of hematopoetic factors for regulating the differentiation of stem cells at p. 32, right column, 2nd full paragraph). Given the strong indications in the art that the CSFs were known to stimulate proliferation of stem cells, it would be obvious to one of ordinary skill in the art at the time the invention was made to culture neural stem cells with the claimed methods. For this reason as well one of ordinary skill in the art could expect success. There is motivation in the art to culture neural stem cells, as they could potentially be used in the treatment of disease associated with neuronal loss. Furthermore, cell culture optimization is routine in the art, and does not represent undue experimentation; scientists are routinely motivated to improve cell culture techniques and there was already strong indications in the prior art that CSFs promote stem cell proliferation coupled with the motivation in the art to culture stem cells. Thus, for the reasons outlined above, the claims do not contribute anything non-obvious over the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

.Claims 1-19, 101-102 and 105 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 9-22 and 52-53 of copending Application No. 10/880,101. Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims are drawn to the same scope and invention, namely, a method of treating a neurological condition in a mammal, comprising administering to the mammal a hematopoietic factor selected from the group consisting of GMCSF, GCSF, derivatives thereof, and combinations thereof in an amount sufficient to treat the neurological condition is selected from the group consisting of a neurological disease with pathophysiological mechanisms involving ischemia, a neurological disease with pathophysiological mechanisms involving hypoxia, a neurodegenerative disease, and a disease of the nervous system accompanied by neural cell death, wherein the neurological disease with pathophysiological mechanisms involving ischemia or hypoxia is stroke, Parkinson's disease, amyotrophic lateral sclerosis, neurotrauma, cerebral ischemia due to cardiac arrest, or cerebral ischemia during an operative procedure, further comprising administering one or more additional hematopoietic factors, wherein

the additional hematopoietic factors are selected from the group consisting of a macrophage stimulating factor, an interleukin, and erythropoietin, administered to the mammal, further comprises administering a hemodynamically active compound, which further comprises administering tPA to the mammal, which further comprises administering an agent that facilitates passage over the blood brain barrier, which further comprises administering an anti-apoptotic agent, wherein the hematopoietic factor is a human factor or derived from a human factor, wherein the mammal is human, wherein the hematopoietic factor is administered by one or more modes of administration selected from the group consisting of direct intracerebral injection, intravenously, intraarterially, orally, and subcutaneously; a method of enhancing the viability of a neural cell culture comprising contacting the neural cell culture with a hematopoietic factor selected from the group consisting of GMCSF, a GMCSF derivative, GCSF, a GCSF derivative, and combinations thereof in an amount sufficient to enhance the viability of the neural cell culture relative to the culture prior to contacting with the hematopoietic factor, wherein the neural cell culture comprises neural stem cells. The only difference between the instant claims and claims 1-5, 9-22 and 52-53 of copending Application No. 10/880,101, is that the claims of the '101 application further recite IL-3 and IL-5. Nevertheless, the scope of the claims of each application overlap and are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER